REMARKS

This paper is responsive to the Office Action dated August 13, 2002 (Paper No. 13), which is the first action on the merits of the application. Claims 57-80 are pending in the application. Claims 47-61, 66, 72, 74-76, 78, and 80 are under examination, and stand variously rejected.

Reconsideration and allowance of the application is respectfully requested.

Claim Objections:

Claims 57, 60, and 61 are objected to as containing subject matter directed to non-elected groups (SEQ. ID NOs:1-3, 5-6, 8, and 10). In another paper, applicants are petitioning against restriction between the sequences. Upon granting the petition, the non-elected SEQ. ID NOs will be rejoined into the subject matter under examination, and this objection will be rendered moot.

Claim 57 is objected to as not ending in a period. This oversight has been corrected in the claim amendments presented above.

Withdrawal of these objections is respectfully requested.

Rejection under 35 USC § 101:

The claims under examination stand rejected under 35 USC § 101 as reading on a process that occurs in nature without requiring the hand of man [or woman].

Without agreeing with this rejection, applicants have amended the claim to require that the polynucleotide be a recombinant polynucleotide, as supported throughout the specification. In accordance with the ordinary meaning of the term, the polynucleotide must be present in the cell in a non-naturally occurring configuration, caused by manipulation by the hand of man.

Withdrawal of this rejection is respectfully requested.

Rejections under 35 USC § 112 ¶ 1:

The claims under examination stand rejected under § 112 ¶ 1 as not being adequately described by the specification.

Applicants respectfully disagree. The "Revised Interim Written Description Guidelines" of the U.S. Patent & Trademark Office indicates that a claim to polynucleotides related by the ability to hybridize to a single representative polynucleotide meets the written description requirements of § 112 ¶ 1. Claim 57 (and its dependents) as previously presented and as amended comport exactly with Example 9 of the guidelines.

The claims also stand rejected under § 112 ¶ 1 on the basis that the specification is enabled for producing a protein from SEQ. ID NO:9, but not from closely related variant polynucleotides that hybridize under stringent conditions to SEQ. ID NO:9.

Applicants respectfully disagree for the following reasons:

- The Office has not established a prime facie case for lack of enablement
- Variants of the representative species (SEQ. ID NO:9) that encode TRRE activity can be made without undue experimentation
- The Office has an established policy of issuing patents with claims covering variants of a single representative species

A: No prima facie case for lack of enablement:

The Patent Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention[1]. This burden has not been met.

In making the rejection, the Office indicates that the specification fails to provide performance parameters of any of the possible [variants] of the protein encoded by SEQ. ID NO:9.

To the contrary. Page 29-34 of the specification provides detailed instructions for a suitable assay for measuring TRRE activity. If a protein has significant activity when measured in this assay, then it will meet the functional requirement of the claim. Variant proteins produced from the polynucleotides indicated, and capable of causing release of TNF receptor from human cells, will fulfill the requirements of the claim. On the other hand, variants that do not cause release of TNF receptor from human cells will fall outside the claim. Accordingly, testable parameters for working variants are provided in the claim, and an exemplary assay is provided in the specification.

The rejection made in the Office Action relies in part on the assertion that it is not possible to predict with absolute certainty which of the variants will work. This assertion is inadequate to support a prime facie case for lack of enablement. Absence of complete predictability only means that the ultimate proving of functional variants is a matter of empirical testing — *not* that such variants are hard to find.

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[1] *In re Wright,* 27 USPQW2d 1510 (Fed. Cir. 1993). It is incumbent upon the Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning. *In re Marzocchi* 169 USPQ 367, 370 (CCPA 1971). The examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. MPEP § 2164.04.

In particular, a paper by Voet et al. (1990) is cited as indicating that a single substitution in a hemoglobin molecule will affect its function. This does not establish a *prima facie* case, because it is only one out of 19 possible variations at one out of 146 possible positions in the hemoglobin molecule. In other words, the paper teaches that one variant (with the Glu at this position) works in a native manner, while one variant (with the Val at this position) works in a different manner. In theory, there are about 2,627 other possible variants with one amino acid change. In addition, the amino acid change upon which the paper focuses is one involving substitution of a charged residue (Glu) with an aliphatic residue (Val). The paper does not discuss, for example, the effect of a conservative amino acid change at this same position. In short, the evidence offered by the Patent Office does not indicate the proportion of the other hemoglobin variants (if any) that lack native activity. Indeed, as far as we know, virtually all of them may work quite well.

Nature provides many illustrations showing that a wide range of alterations are tolerated at almost all positions of working proteins. Protein sequences are typically *only ~70% identical* between different mammalian species. This indicates that a wide range of substitutions are possible without affecting function. Indeed, there is no reason why the skilled reader could not make any number of functional variants of TRRE that they desire.

B: Variants may be obtained by routine experimentation

There are a number of methods available to construct variants of the TRRE sequence. The Office Action implies that the user would want to create variants by making deliberate changes to SEQ. ID NO:9, as described above. Deliberate point mutations are sometimes made when the investigator wants to map functional elements within the primary protein structure.

Although the reader may wish to make variants by mutation at particular sites, it is unnecessary for them to do so. Where the object is only to generate functionally equivalent variants, the skilled reader can employ a random mutation strategy, which is even more straightforward. There is an enormous literature in the art relating to introducing mutations of various kinds. The standard texts *Protocols in Molecular Biology* (Ausubel et al. eds.) and *Molecular Cloning: A Laboratory Manual* (Sambrook et al. eds.) describe techniques employing chemical mutagenesis, cassette mutagenesis, degenerate oligonucleotides, mutually priming oligonucleotides, linker-scanning mutagenesis, alanine-scanning mutagenesis, and error-prone PCR. Other efficient methods include the *E. coli* mutator strains of Stratagene (Greener et al., Methods Mol. Biol. 57:375, 1996) and the DNA

shuffling technique of Maxygen (Patten et al., Curr. Opin. Biotechnol. 8:724, 1997; Harayama, Trends Biotechnol. 16:76, 1998).

The mutated variants can then be cloned out and tested for functionality as described in the specification. To the extent that the user may wish to test variants near the outer limit of variability in the claims (i.e., only ~90% identical to SEQ. ID NO:9), they may subject the representative sequence to successive cycles of mutation and functional testing — or choose a mutation strategy that generate more abrupt changes, such as the DNA shuffling technique.

To what extent will the variants produced by these techniques have the required functional activity? The Office Action cites *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) as setting the standard for unreasonable experimentation. In fact, the patent under consideration in *Wands* was found to be *enabling* for production of the genus of monoclonal antibodies having the specificity and affinity claimed[2]. The screening of TRRE variants for function according to the present invention is routine in the same manner as testing hybridoma clones for secretion of antibody with particular characteristics.

In summary, generating variants of the representative sequence SEQ. ID NO:0 can be done by standard techniques in the art. The variants can be tested for functionality by a number of suitable assays, such as those described in the specification. The evidence of record in this application and presented in this Response implies that a substantial proportion of these variants will have TRRE catalytic activity, and can be made and identified without undue experimentation.

C: The Office has an established policy of allowing coverage for closely related sequences

As referred to earlier, the "Revised Interim Written Description Guidelines" indicates that polynucleotide sequences claimed according to their ability to hybridize to a representative sequence fall within the description requirements of 35 USC § 112 ¶ 1. It is inconceivable that the Office would have promulgated these Written Description Guidelines knowing that this illustration complied with the description requirements of § 112 ¶ 1, but not the enablement requirements of the very same statute.

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[2] In *Wands*, the patent application claimed monoclonal antibodies of a particular specificity and affinity. The PTO contended that only 2.8% of the hybridomas obtained were proven to fall within the claim, and thus the claim was not enabled. *The Court held that the application was fully enabled for the claimed subject matter,* because it was standard practice to screen negative hybridomas in order to find one that makes the desired antibody. 8 USPQ2d at 1406-07.

At the time of this writing, there are approximately 1,946 issued U.S. patents that have the words "stringent" and "hybridize" or "hybridization" in the claims. The Office is especially invited to consider U.S. Patent 6,413,741, which issued this past July. Claim 1 covers nucleic acid encoding a polypeptide monomer that has the ability to form, with at least one additional alpha subunit, a potassium channel having the characteristic of voltage gatin, wherein said nucleic acid specifically hybridizes under [specified] stringent conditions to SEQ ID NO:2. The face of the patent indicates that Examiners Joseph F. Murphy and David S. Romeo allowed these same claims to issue.

It would be unfair to hold applicants of the present application to only the exact sequence obtained. This would give competitors an easy way to steal the essence of applicants' discovery simply by making a close functional variant with one or more mutations in the sequence. The objective would be not to improve the properties of the molecule, but simply to evade applicants' patent protection.

The case law provides the following commentary on the public policy reasons for allowing applicants reasonable claim scope beyond the species explicitly disclosed:

> To require such a complete disclosure [of all the species claimed] would apparently necessitate a patent application or applications with thousands of catalysts . . .More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used . . ."[3]

The TRRE sequences provided in this disclosure represent a new discovery of important new gene family with important biological activity. The coverage scoped out by the claims in the present application circumscribe a reasonable area of coverage that is necessary to adequately protect against easy and insubstantial work-around variants — in full accordance with the standard set in *In re Angstadt.*

Withdrawal of the rejections under 35 USC § 112 ¶ 1 is respectfully requested.

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[3] *In re Angstadt,* 190 USPQ 214 at 218 (CCPA 1976)

Rejections under 35 USC § 112 ¶ 2:

The claims under examination stand rejected under 112 ¶ 2 as being indefinite for not providing a clear functional limitation. This oversight has been corrected in the amendment to claim 57 presented above. The functional limitation is supported by the claims as originally presented, and throughout the specification. No new matter is added. Applicants thank the Examiner for pointing out this error.

The claims also stand rejected for not specifying what is meant by the term "stringent hybridization". Applicants respectfully disagree, since the term is defined on page 11 of the specification. Nevertheless, as a courtesy to the reader, the hybridization conditions have been explicitly incorporated into claim 57. Since this does not change the definition of the term, coverage is maintained for all equivalents of the claimed subject matter for which applicant was previously entitled.

Withdrawal of these rejections is respectfully requested.

Conclusion

Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicants hereby requests an interview by telephone. The Examiner is further invited to telephone the undersigned should he believe that such would expedite prosecution.

In the event that the transmittal letter is separated from this document and the Patent Office determines that extensions or other relief is required and/or fees are due applicants, the Applicant petitions for any required relief, including extensions of time, and authorize the Commissioner to charge our Deposit Account No. 50-0815, Order Number IRVN-007CIP2, for any fees due in connection with the filing of this document. The Patent Office is not authorized to charge issue fees to our Deposit Account.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Feb 13, 2003

By: Carol L. Francis
Carol L. Francis
Registration No. 36,513

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231
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